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ORIGINAL ARTICLE

Phase II study of first-line biweekly docetaxel and cisplatin combination chemotherapy in advanced gastric cancer

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Abstract
Purpose Previous studies have shown that docetaxel and cisplatin, as single agents, are effective and relatively well tolerated in patients with advanced gastric cancer. The aim of this study was to assess efficacy and toxicity of a biweekly regimen of docetaxel plus cisplatin in patients with advanced gastric cancer.
Patients/methods Fifty-five patients with histologically proven advanced gastric cancer with at least 1 measurable lesion and ECOG PS ≤ 2 were enrolled. Patients received docetaxel 50 mg/m^2 and cisplatin 50 mg/m^2 every 2 weeks until progression disease, unbearable toxicity or a maximum of 12 cycles.
Results In total, 426 cycles were administered (median 8.5 cycles) to 52 evaluable patients. One patient (1.9 %) showed a complete response, while 21 (40.4 %) had partial responses. The objective response rate was 42.3 % (95 % CI 28.9–55.7), the median time to progression was 5.5 months (95 % CI 4.0–7.0), and the median overall survival was 8.9 months (95 % CI 6.0–11.9). The most common grade 3–4 toxicities per cycle were haematological [neutropenia (5.9 %)].
Conclusions Biweekly administration of docetaxel and cisplatin in advanced gastric cancer has a manageable toxicity profile and shows a promising antitumour activity as a first-line therapy.

Keywords Advanced gastric cancer · Cisplatin · Combination chemotherapy · Docetaxel

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Introduction

Gastric cancer (GC) is the fourth most common cancer worldwide (7.8 % of cancers) and the second most frequent cancer-related cause of death (9.7 % of cancer deaths). Approximately half of new gastric cancer cases occur in East Asia [1].

In Western countries, 80–90 % of patients are usually either diagnosed at an advanced inoperable disease or develop recurrence within 5 years after surgery with curative intention [2]. Advanced gastric cancer patients have a poor prognosis with a median survival time, for those untreated, of 3–5 months. The 5-year survival for advanced/metastatic gastric cancer is <10 %, and, despite the recent development of new chemotherapy regimens and the introduction of biologic therapy, median overall survival (OS) remains <1 year [3].

Combined chemotherapy is still the standard first-line treatment for advanced gastric cancer as there is strong evidence for an improvement in patient outcomes in advanced gastric cancer compared with single-agent chemotherapy (HR for survival of 0.82; 95 % CI 0.74–0.90) according to a recent meta-analysis [2]. However, there is a great variability in the regimens administered [4–8].

Furthermore, in spite of the advances during the past decade with regard to GC therapy, through the combination of new drugs such as docetaxel (D), irinotecan and oxaliplatin, which have provided more effective and better

tolerated regimens for the treatment of advanced gastric cancer [9], treatment remains unsatisfactory in terms of response rate, response duration, toxicity, convenience and overall survival benefit in patients with advanced gastric cancer.

In Europe and the USA, fluoropyrimidine–platinum-based combinations with or without the addition of a third drug, typically docetaxel or epirubicin (E), are the most widely used chemotherapy combinations for advanced gastric cancer first-line treatment. The evidence to support the activity of an anthracycline-based triplet [i.e. epirubicin, cisplatin and 5-fluorouracil (ECF)] is provided by two randomized studies, refs. [7, 8]. However, there is also some uncertainty regarding the value of adding an anthracycline from trials which did not demonstrate a benefit with the anthracycline triplet therapy over the doublet chemotherapy [10, 11].

In Western countries, docetaxel is the preferred agent for use in combination with CF (i.e. DCF), based on the V325 trial in which improved survival was observed with DCF compared with CF (HR 0.77; $p = 0.02$) [12]. The DCF regimen was, however, associated with excessive toxicity, particularly myelosuppression with a 29 % incidence of febrile neutropenia. DCF is thus typically administered in patients with good PS. Various modified DCF regimens are being investigated to reduce toxicity while maintaining activity [13–16].

Different regimens combining docetaxel with cisplatin yielded response rates of 37–56 %, and also provided evidence about good treatment tolerability, despite their haematotoxicity [17–20]. Non-haematological toxicity including nausea/vomiting and alopecia has been rarely severe in these studies [17–21]. Similar activity was observed with the administration of docetaxel in combination with 5-FU [22]. All these studies showed that the combination of docetaxel and cisplatin is an active and relatively well-tolerated regimen according to the dose used.

Overall, these results offer new alternatives to the treatment of advanced gastric cancer. The modification of the cisplatin–docetaxel schedule may yield a regimen with an improved safety profile without compromising the efficacy of the regimen.

This phase II study was designed to assess the efficacy and toxicity of a first-line treatment, based on biweekly docetaxel plus cisplatin, in patients with advanced gastric cancer.

Patients and methods

This study was a phase II, open-label, one-arm, multicentre, and clinical trial. The study was approved by the Local Research Ethics Committees and in accordance with the Declaration of Helsinki, the Good Clinical Practices, and local ethical and legal requirements. All patients, enrolled from five Spanish sites, signed informed consent.

Patient selection

Patients aged ≥18 years with histologically confirmed locally advanced or metastatic and inoperable gastric cancer—including gastroesophageal junction cancer—were considered for enrolment in the study. Other eligibility criteria included measurable disease according to RECIST criteria v1.0; no prior palliative chemotherapy; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; life expectancy of more than 12 weeks and adequate bone marrow, renal and hepatic function. Major exclusion criteria included clinical evidence of brain metastases; history of any malignant process within the last 5 years except basocellular skin tumours and carcinoma in situ of cervix; previous history of uncontrolled cardiomiopathy and history of neurological toxicity grade ≥2.

Prior to enrolment, all patients underwent a clinical assessment including medical history, physical examination and imaging studies (computed tomography of thorax and abdomen, abdominal ultrasound, chest X-ray in two planes). Haematology and chemistry were also assessed before study entry and on a regular basis during and after treatment. Tumours were diagnosed and staged according to the American Joint Committee on Cancer/TNM staging classification for carcinoma of the stomach, sixth edition (2002) [23].

All patients with these characteristics were enrolled in the trial.

Response and toxicity assessments

Every three cycles of treatment, a computed tomography of thorax and abdomen, or the imaging technique initially used to determine the tumour, was performed in each patient. Abdominal ultrasound alone was not accepted as the only method for evaluating the evolution of the tumour.

The RECIST criteria v1.0 were followed to assess the type of response. Adverse events were assessed through the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) v2.0, respectively. During the first two cycles of treatment, toxicity was assessed every week.

Drug administration

Chemotherapy consisted of docetaxel 50 mg/m^2 and cisplatin 50 mg/m^2. Both drugs were administered by intravenous infusion over 1 h on day 1. Docetaxel was diluted in either 100, 250 or 500 cc of normal saline or 5 % glucose solution and cisplatin in 500 cc of normal saline along with

500 cc of manitol. Treatment was repeated every 2 weeks until a maximum of 12 cycles (24 weeks of treatment) that could be extended on an individual basis at clinician discretion. Patients were withdrawn from further protocol treatment if tumour progression or unacceptable toxicity occurred.

All patients received a standard supportive regimen consisting of hyperhydration (1 l of 0.9 % normal saline plus 10 mEq of potassium chloride and magnesium sulphate (Sulmetin®) 10 mL by intravenous infusion over 1 h) and dexamethasone 8 mg p.o. or i.v. administered 12 and 6 h before docetaxel infusion. 5-HT_3 inhibitors were used for emesis prophylaxis. The hyperhydration regimen was administered before and after chemotherapy administration and could be modified on individual basis to fit patients' characteristics. The use of loop diuretics for the prevention of cardiovascular complications was allowed.

Docetaxel and cisplatin were administered according to the pre-established schedule provided that neutrophils count $\geq 1.5 \times 10^9$, platelet count $\geq 100 \times 10^9$ and no grade ≥ 2 non-haematological toxicity, except alopecia and vomiting, did not occurred. The doses of docetaxel and/or cisplatin were reduced by 20 % if any grade 4 haematological toxicity occurred. If febrile neutropenia and/or neutropenia and or thrombocytopenia occurred, both docetaxel and cisplatin dosages were reduced by 20 %. The next cycle of treatment could be delayed up to 3 weeks until toxicities resolution. Patients were withdrawn from the study for any treatment delay longer than 3 weeks.

In case of creatinine clearance <40 mL/min and/or creatinine >2.0 mg/dL, the next cycle of treatment was delayed for 1 week, and if no recovery to creatinine clearance >40 mL/min and/or creatinine <2.0 mg/dL after 7 days, cisplatin was discontinued. A 75 % dose reduction in docetaxel was mandatory in case of grade ≥ 2 liver toxicity. When the values of ALT/AST and alkaline phosphatase were >5 times the UNL, the treatment administration was delayed for 2 weeks and, if no recovery was observed, the treatment was discontinued. In case of grade ≥ 2 peripheral neuropathy, the dose of docetaxel was reduced by 20 % along with a 50 % reduction in cisplatin dose. In case of other grade 3/4 toxicities, except alopecia and nausea/vomiting, the dose of the suspected drug was reduced by 20 %.

After completion of 12 cycles of treatment or discontinuation of chemotherapy, disease status was re-evaluated every 3 months.

Concomitant treatment

Palliative radiotherapy could be administered if a pre-existing lesion became more painful. However, if palliative radiotherapy was needed for the treatment of a second pre-existing lesion, the treatment was to be discontinued since this was considered as a disease progression.

Granulocyte colony-stimulating factor (G-CSF) was allowed when febrile neutropenia appeared.

Statistical methods

The sample size for the study, not statistically predetermined, was 55 patients. Efficacy analyses were performed including those patients evaluable for response, i.e. patients who received, at least, one cycle of study treatment and were evaluated for response once, at least, after the first treatment cycle. Safety analysis included all patients who have received at least one dose of study treatment.

The study endpoints were objective response rate [ORR: complete response (CR) + partial response (PR)], overall survival (OS) and time to progression (TTP).

The data are presented using descriptive statistics. Continuous variables are expressed as mean, standard deviation, median and range (minimum–maximum). The 95 % confidence interval (95 % CI) was calculated for each response rate. CRs or PRs had to be confirmed four or more weeks after the initial one. Time-dependent variables were estimated with the Kaplan–Meier method. TTP was defined as the time from enrolment to progression or death. Time of survival was calculated from the enrolment date to the time of death or last follow-up. All statistical analyses were carried out by using SPSS version 15.0 (SPSS, Chicago, Illinois, USA).

Results

A total of 55 patients were enrolled. Three out of 55 patients were not evaluable, and only baseline data were recorded. One of them was lost to follow-up, other of them suffered a deterioration in overall condition, and another one died as a result of toxicity. The aim centre included 19 evaluable patients, and the other four centres included a total of 33 patients (second centre 15 patients, third 9 patients, fourth 5 patients and fifth 4 patients). These differences in recruitment are derived from the different incidences of gastric cancer in our geographic region. Most of the patients were male (37; 71.2 %), and the median age of the patients was 66 years (range 37–84 years). Thirty-six patients (78.3 %) and 7 patients (15.2 %) had an ECOG PS of 1 and 2, respectively. Twenty-three patients (44.2 %) had metastases. The main metastatic sites included abdominal lymph nodes, liver, retroperitoneal lymph nodes, adrenal glands and lung. Twenty patients (38.5 %) had undergone a surgical resection of their primary tumour (total or subtotal gastrectomy), and 10 had received neoadjuvant chemotherapy (6 patients received 5-FU/leukovorin (LV),

2 received 5-FU/cisplatin, 1 received 5-FU/cisplatin/LV and 1 received docetaxel). Five patients (9.6 %) had previously received radiotherapy. The median time from diagnosis to administration of the first cycle of treatment was 1.3 months ($n = 49$; range 0.03–181.9 months) (see Table 1).

Treatment administration

Treatment with docetaxel and cisplatin was well tolerated. Four hundred and twenty-six cycles of treatment were administered with a median of 8.5 cycles per patient, and 14 patients (26.9 %) completed the planned 12 cycles of treatment. One hundred cycles were delayed (23.5 %): 26 as a result of haematological toxicity, 1 due to non-haematological toxicity, 1 as a consequence of both haematological and non-haematological toxicities, 6 for other reasons unrelated to the treatment and 66 for unspecified reasons. The dose was reduced in 9 cycles (2.1 %): 2 cycles as a result of haematological toxicity, 2 due to non-haematological toxicity and in 5 cycles the cause was not reported. The median relative dose intensities were 92 and 90 % for docetaxel and cisplatin, respectively.

Efficacy

One out of 52 evaluable patients (1.9 %) achieved a CR, and 21 (40.4 %) achieved a PR. Fourteen patients (26.9 %) had a stable disease with at least seven cycles of treatment. The median follow-up time was 7.7 months. Disease progression was observed in 13 patients (25 %). The ORR was 42.3 % (95 % CI 28.9–55.7). There was no statistically significant difference in response according to the number of disease sites (Table 2). The median TTP was 5.5 months (95 % CI 4.5–6.5) (Fig. 1). At 6 months, 42 % (95 % CI 28.1–55.9) of the patients did not have progression disease. The median OS was 9.5 months (95 % CI 7.1–12) (Fig. 2), and 68.6 % (95 % CI 55.5–81.7) of the patients were alive at 6 months.

Safety

Fifty-two patients received at least one cycle of the study treatment. A total of 426 chemotherapy cycles were administered, and 14 patients (26.9 %) completed the planned 12 cycles of treatment. Thirty-eight patients discontinued the study therapy; 20 as a result of disease progression, but only 2 patients progressed immediately after the first cycle of treatment. One patient, who experienced grade 2 anaemia and grade 1 dysfagia, decided to discontinue voluntarily chemotherapy after cycle 8 due to toxicity. One patient withdrew the study after cycle 4 due to poor family support, and another one was withdrawn from the study after having experienced a severe general deterioration with cycle 2. One patient could not be treated as a result of a severe allergic reaction to cisplatin. Six patients (11.5 %) died while they were under treatment. Five of them died of progressive disease and 1 as a result of haematological toxicity after having experienced grade 3 thrombocytopenia and grade 4 neutropenia. Two patients were lost to follow-up, and the reason for the treatment discontinuation was not reported for two other patients.

Grade 3–4 events were infrequent (Tables 3, 4). The most frequent grade 3 and 4 haematological toxicity was neutropenia, which was reported in 16 patients (30.8 %). No patient showed febrile neutropenia.

Centre	*N*	%
Hospital Xeral Calde	19	36.5
Hospital Xeral-Cies	15	28.8
Hospital Meixoeiro	9	17.3
Hospital Santa Maria Nai	4	7.7
Complejo Hospitalario de Santiago	5	9.6
Total	52	100

Distribution of patients by centre

Table 1 Baseline patient and tumour characteristics (evaluable patients)

Patient characteristics	$n = 52$
Age (years)	
Median	66
Range (min–max)	37–84
Sex [*n* (%)]	
Male	37 (71.2)
Female	15 (28.8)
Weight (kg)[a]	
Median	63
Range (min–max)	41–85
Height (cm)[b]	
Median	163
Range (min–max)	147–183
Body surface (m^2)[c]	
Median	1.7
Range (min–max)	1.4–2.0
ECOG [*n* (%)][d]	
0	3 (6.5)
1	36 (78.3)
2	7 (15.2)
Disease sites [*n* (%)][e]	
Stomach	24 (47.1)
Liver	23 (45.1)
Lymph nodes	22 (43.1)

Table 1 continued

Patient characteristics	$n = 52$
Peritoneum	8 (15.6)
Suprarenal	3 (5.9)
Lung	3 (5.9)
Coeliac	1 (2.0)
Kidney	1 (2.0)
Number of disease sites per patient [*n* (%)][f]	
1	28 (54.9)
2	11 (21.6)
≥3	12 (23.5)
Number of lesions per patient [*n* (%)][g]	
1	23 (45.1)
2	12 (23.5)
≥3	16 (31.3)
Primary tumour stage [*n* (%)]	
IA	1 (1.9)
IB	1 (1.9)
II	2 (3.8)
IIIA	1 (1.9)
IIIB	3 (5.8)
IV	39 (75.0)
Not specified	5 (9.6)
Prior therapy [*n* (%)]	
Radiotherapy	5 (9.6)
Surgery	20 (38.5)
Chemotherapy	10 (19.2)

[a] Not available in three patients

[b] Not available in four patients

[c] Not available in one patient

[d] Not available in six patients

[e] If two or three lesions were in the same site, it was considered as only one disease site. In one patient, this information was not collected ($n = 51$)

[f] Number of lesions per patient independently of the number of lesions in each organ. In one patient, this information was not collected ($n = 51$)

[g] Number of lesions per patient independently of the organ where they are found. In one patient, this information was not collected ($n = 51$)

Discussion

Advanced gastric carcinoma has very poor prognosis, with different active chemotherapy combinations, though the treatment in this stage is still palliative.

Five centres of a north-west region of Spain conducted a prospective trial to asses the efficacy and tolerability of a biweekly combination of cisplatin and docetaxel, two of the most active chemotherapeutic agents for this disease, in an effort to establish a better tolerated but efficacious regimen.

The population of the study is heterogeneous including patients with the primary tumour resected (38.7 %), a high proportion with unresectable locally advanced gastric cancer (44 %) and ten of them who had received neoadjuvant chemotherapy treatment.

The distribution of the hospitals included two centres with mostly rural population, and three of them urban population. This is the usual living image of the real scenario of the clinical practice, and ours results.

The lack of control arm and data of the reasons of exclusion for patients not included and the treatment used in those patients do not allow us to establish this regimen as a standard for our patients.

However, this phase II clinical trial provides evidence that docetaxel plus cisplatin, at biweekly doses of 50 mg/m^2 each, is active in advanced gastric cancer. The observed ORR in this trial (42.3 %; 95 % CI 28.9–55.7) was higher to those reported ORRs for DC and DCF arms from the phase II/III V325 trial (DC: 26 %; 95 % CI 17–38 %; DCF: 37 %; 95 % CI 30.3–43.4) [12, 24]. Furthermore, in that trial the median TTP was 5.6 months (95 % CI 4.9–5.9) for DCF and 5.0 months for DC (95 % CI 3.7–6.3), and the median OS times were 9.2 months (95 % CI 8.4–10.6) for DCF and 10.5 months (95 % CI 9.5–12.9) for DC. In our trial, the corresponding median TTP and OS were very similar to the above mentioned, 5.5 (95 % CI 4.5–6.5) and 9.5 months, respectively. In addition, our results are very similar to those obtained with other second-generation combinations such as etoposide/adriamycin/cisplatin (EAP), 5-FU/adriamycin/methotrexate (FAMTX), 5-FU/cisplatin (FUP),

Table 2 Type of response according to the number of disease sites

	CR [*n* (%)]	PR [*n* (%)]	SD [*n* (%)]	DP [*n* (%)]	Lost to follow-up [*n* (%)]	Total [*n* (%)][a]
Number of disease sites						
1	1 (100.0)	11 (52.4)	8 (57.1)	8 (61.5)	0 (0.0)	28 (54.9)
2	0 (0.0)	5 (23.8)	2 (14.3)	4 (30.8)	0 (0.0)	11 (21.6)
3	0 (0.0)	5 (23.8)	4 (28.6)	1 (7.7)	2 (100.0)	12 (23.5)
Total	1 (100.0)	21 (100.0)	14 (100.0)	13 (100.0)	2 (100.0)	51 (100.0)

SD stable disease, *DP* disease progression

[a] Data about disease sites were not recorded in one patient

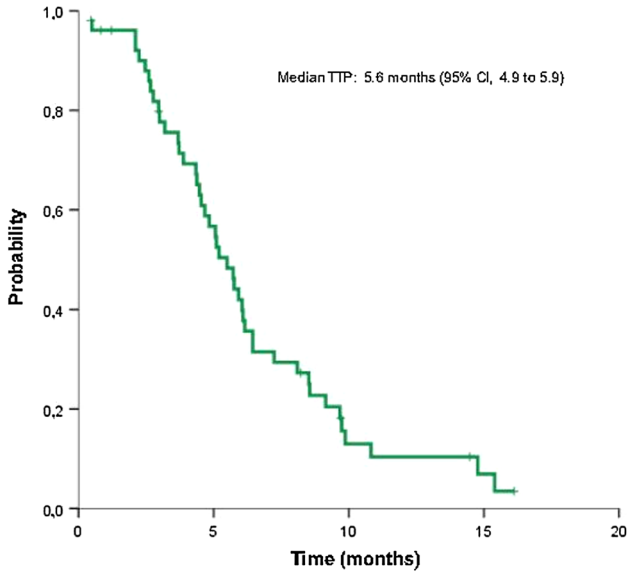

Fig. 1 Time to progression

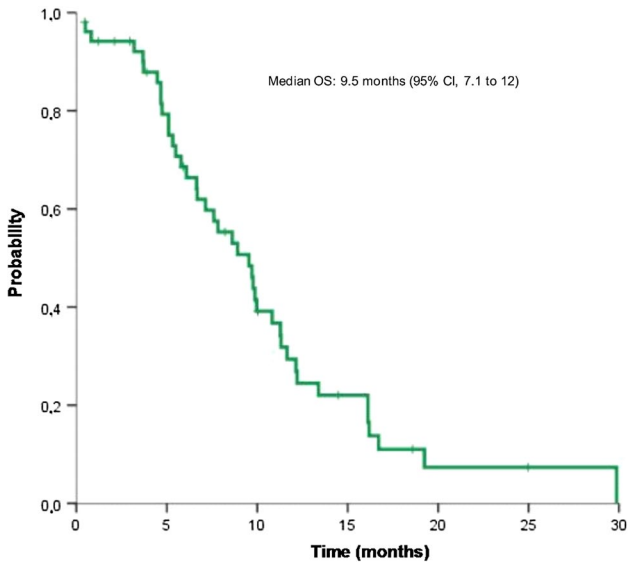

Fig. 2 Overall survival

etoposide/leukovorin/5-FU (ELF), epirubicin/cisplatin/5-FU (ECF) or cisplatin/epirubicin/leukovorin/5-FU (PELF) [7, 25–28].

The combination was generally well tolerated, with a median of 8.5 cycles of treatment given per patient, and grade 3 and 4 neutropenia observed in 11 (21.2 %) and 5 (9.6 %) patients, respectively. However, no cases of febrile neutropenia were observed. In addition, even though there were 6 deaths during the treatment period, only 1 was

Table 3 Haematological toxicity

Toxicity	Patients [*n* (%)]		Cycles [*n* (%)]	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	3 (5.8)	0 (0.0)	7 (1.6)	0 (0.0)
Neutropenia	11 (21.2)	5 (9.6)	17 (4.0)	6 (1.4)
Thrombocytopenia	2 (3.8)	0 (0.0)	3 (0.7)	0 (0.0)

Table 4 Non-haematological toxicity

Toxicity	Patients [*n* (%)]		Cycles [*n* (%)]	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	2 (3.8)	0 (0.0)	3 (0.7)	0 (0.0)
Vomiting	2 (3.8)	1 (1.9)	3 (0.7)	1 (0.2)
Diarrhoea	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)
Mucositis	1 (1.9)	0 (0.0)	1 (0.2)	0 (0.0)
Oedema	2 (3.8)	0 (0.0)	2 (0.5)	0 (0.0)
Cutaneous lesion	1 (1.9)	0 (0.0)	1 (0.2)	0 (0.0)
Asthenia	4 (7.7)	1 (1.9)	4 (0.9)	3 (0.7)
Hypersensitivity	1 (1.9)	1 (1.9)	1 (0.2)	1 (0.2)

related to the study treatment. Therefore, these results suggest that the safety profile of the study regimen is similar or even better than other reported combinations such as ECF, ECD, DCF, PELF and FAMTX [25, 29–31]. The combination used in this trial is also advantageous in terms of not requiring the regular use of G-CSF. These safety results are also favourably in comparison with the toxicity results reported from other similar studies where doses of docetaxel and cisplatin were higher [19, 21, 25], probably related to the lower doses of cisplatin and docetaxel used in this study.

Although the small of the trial sample size as well as the design preclude establishing definitive conclusions, the study results suggest that biweekly docetaxel plus cisplatin at doses of 50 mg/m^2 each produce an important clinical benefit in patients with advanced gastric cancer with a manageable toxicity profile. These observations should be confirmed in future controlled randomized clinical trials, including quality-of-life assessment, that allow evaluating the real advantages of this regimen.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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